Tdap

Pertussis has been a source of frustration for both public health and private providers for several years. The disease is difficult to diagnose, difficult to treat, and seems to be increasing despite our best efforts to control it. This graph shows the number of reported cases by year since 1980, when only about 1,700 cases were reported. There are cyclic peaks every 3 to 5 years, but the number of cases reported has been steadily increasing. A total of 11,647 cases was reported in 2003, the highest annual total since 1964. The provisional total for 2004 was even higher – more than 18,000 reported cases.

Adolescents with pertussis are increasingly reported across the United States. This graph shows the number of pertussis cases reported by age group and year since 1990. Cases among adolescents 11 through 18 years of age are highlighted in yellow. Notice the increasing proportion of cases reported in this age group in the last 15 years. In 2003 adolescents 11 through 18 years of age accounted for 36% of all reported cases. In 2004, about 8,000 of the reported cases were among children in this age group.

One factor that may be contributing to the rise in pertussis among older children and adults is waning vaccine induced immunity. Protection declines as you get further away from the time you had your last dose. After 5 to 10 years, vaccine induced immunity is probably minimal. At this point, even vaccinated persons may become infected and develop mild or undiagnosed disease, which could then be transmitted to incompletely vaccinated infants.

The impact of pertussis among adolescents is significant. The illness can have a prolonged cough that can last for more than 3 months. Most adolescents have loss of sleep, about half experience post-tussive vomiting after a severe paroxysm of cough. A small percentage of adolescents lose consciousness during these paroxysms. About one third lose weight during the illness. Complications of pertussis among adolescents include pneumonia in 2%, rib fractures from violent coughing in one percent, and about one percent of adolescents with pertussis are hospitalized. The medical costs, missed school and work, and impact on the public health system all contribute to the personal and societal burden of pertussis among adolescents.

Pertussis is one of a few bacterial infections for which antibiotic treatment has little effect on the course of the illness. Treatment lessens the severity of pertussis if given early in disease, before the cough is well established. However, this is usually before the illness is recognized as pertussis.

Vaccination is the most effective strategy to reduce the burden of pertussis. Economic studies of the impact of pertussis among adolescents suggest that a vaccination program for adolescents would be an effective strategy, and is likely to be cost effective as well. On June 30, 2005 the Advisory Committee on Immunization Practices – ACIP – voted to establish a vaccination program for adolescents. This program is intended to protect adolescents against pertussis as well as tetanus and diphtheria.

The primary objective of the adolescent vaccination program is to protect vaccinated adolescents against pertussis. The secondary objective is to reduce the reservoir of *Bordatella pertussis* in the population, and thereby potentially reduce the incidence of pertussis in other age groups.

Two manufacturers have licensed Tdap vaccines that contain acellular pertussis antigens. Both vaccines contain a reduced quantity of pertussis antigen compared with pediatric pertussis vaccines. The quantity of tetanus and diphtheria toxoids is similar to available adult Td formulations. Both these reduced antigen vaccines are approved by FDA for use in adolescents. Boostrix® Tdap vaccine is manufactured by GlaxoSmithKline. It was licensed May 3, 2005 for use as a single dose in persons 10 through 18 years of age. Adacel™ Tdap vaccine is manufactured by sanofi pasteur. Adacel was licensed June 10, 2005 for use as a single dose in persons 11 through 64 years of age. Both Tdap vaccines are approved by the Food and Drug Administration as a single booster dose in persons who have previously received a full series of 4 or 5 doses of pediatric DTaP or DTP. These vaccines are **not** approved for use as a primary series, or for persons who have not completed a full series of DTaP or DTP. We will come back to this issue in a moment. Neither vaccine contains thimerosal as a preservative.

We would like to now summarize the June 30, 2005 ACIP recommendations for use of Tdap and Td vaccines. These recommendations **only** apply to adolescents 11 through 18 years of age. Please note that these recommendations are provisional. ACIP recommendations do not become official until approved by the Director of CDC, the Department of Health and Human Services, and have been published in CDC's *Morbidity and Mortality Weekly Report.* Some changes should be expected.

A few general principles apply to the use of Tdap and Td in adolescents. The recommendations address vaccination to protect against tetanus, diphtheria *and* pertussis. For adolescent recommendations, Tdap from the two manufacturers can be considered interchangeable. ACIP has not stated a preference for one product over another. In most situations, Tdap is preferred to Td to provide protection against pertussis. As we mentioned earlier, Tdap is licensed only for a single dose at this time. Future studies will address the immunogenicity and safety of subsequent doses, for example, a second or third dose.

Before discussing the specific recommendations it will be useful to review the current Recommended Childhood and Adolescent immunization schedule, dated

January 2005. The last two columns on the right highlighted in yellow show the recommended Td booster at the 11 through 12 year visit. Shown in green is the recommended catch-up Td booster for adolescents 13 through 18 years who missed the dose scheduled for the 11-12 year visit. The new ACIP recommendation is that adolescents 11 through 12 years of age should receive a single dose of Tdap instead of Td if they have completed the recommended childhood DTaP vaccination series, and have not yet received a Td booster. The ACIP also recommends that adolescents 13 through 18 years who have not received Tdap should also receive a single dose of Tdap as their catch-up booster instead of Td, if they have completed the recommended childhood DTaP vaccination series, and have not received Td.

Some adolescents 11 through 18 years may already have received a Td booster. The ACIP encourages adolescents who received a Td booster to receive a single dose of Tdap to provide protection against pertussis, if they have completed the recommended childhood DTaP vaccination series. A 5-year interval between the Td and Tdap is encouraged to reduce the chance of a local reaction. However, this 5-year interval between Td and Tdap is not set in stone. The two vaccines can be separated by intervals shorter than 5 years. The benefits of protection from pertussis should generally outweigh the risk of a local reaction in settings with increased risk from pertussis. These settings might include a pertussis outbreak in the community or having an infant in the household. Two Canadian studies evaluated local reactions in more than 6,000 students who received Tdap at various intervals after they had already received Td or 5 doses of DTP. Intervals as short as two years were found to be acceptably safe. The ACIP did not define an absolute minimum interval between a dose of Td and a subsequent dose of Tdap, to give maximum flexibility to providers. The provider will need to decide when to administer Tdap based on whether the benefit of pertussis immunity outweighs the hypothetical increase in risk of a local adverse reaction – a sore arm.

As you know, ACIP recommends the administration of all indicated vaccines at the same visit. This fundamental vaccination strategy increases the likelihood that a person will receive each of the vaccines recommended for his or her age or situation. There are two issues that relate to simultaneous and nonsimultaneous administration of vaccines at the adolescent visit. As we discussed earlier, meningococcal conjugate vaccine, or MCV, is now recommended for all adolescents at the 11-12 year visit. ACIP recommends that providers administer Tdap and MCV to adolescents during the same visit, if both vaccines are indicated and available. Meningococcal conjugate vaccine contains diphtheria toxoid as its carrier protein. The amount of diphtheria toxoid in MCV is similar to that in pediatric DTaP. Tdap, Td and MCV induce antibody responses to diphtheria, although MCV is **not** indicated for immunization against diphtheria. There is concern that the risk of a local reaction could be increased when two diphtheria-containing vaccines are administered within a short interval, such as a few days apart. Schedules administering Tdap and MCV in various sequences are being studied now. To date, acceptable rates of local reactions have been found in clinical studies of Td and MCV administered simultaneously; Td followed

one month later by MCV; and MCV followed 3 years later by a second dose of MCV. During the period when Tdap is being introduced and may not be available in all offices and clinics, it might not be possible to give Tdap and MCV simultaneously. ACIP and the Tdap Working Group discussed this issue at length. Immunity to both pertussis and meningococcus is very important for adolescents, and no evidence to date indicates that nonsimultaneous administration of these two vaccines is harmful. As a result, the provisional ACIP recommendation is that if simultaneous administration of MCV and Tdap is not feasible, these vaccines can be administered at any time before or after each other. There is no absolute minimum interval recommended between these two important vaccines. Obviously, this issue will continue to be studied.

Another issue concerning simultaneous administration of vaccines to adolescents is the administration itself. Providers need to be aware that syncope can occur after vaccination and may be more common among adolescents. Be sure to have the adolescent sit down when being vaccinated. You may also want to consider a 15 to 20 minute observation period after vaccination, as discussed in the 2002 *General Recommendations on Immunization*.

Many providers have not yet received a supply of Tdap. One of the most common questions we have received since the licensure of Tdap has been whether or not to defer a scheduled dose of Td in anticipation of Tdap becoming available in the office in the near future. Allowing a person to leave your office having intentionally **not** administered a recommended vaccine is generally not something you do. But until Tdap becomes more widely available it may be necessary for us to make an exception to this rule.

Providers may defer a scheduled dose of Td in anticipation of the availability of Tdap if the following conditions are met: the last dose of tetanus containing vaccine was administered within the last 10 years, **and** the person does not need immediate protection from tetanus – because of a wound, for instance – **and**, in the provider's opinion the person is likely to return for a subsequent visit when Tdap is available. In this circumstance, providers should maintain a system to recall the adolescent when Tdap is available. As we mentioned earlier, both Tdap vaccines are approved as a single booster dose among persons who have completed a series of pediatric DTaP or DTP vaccine. Technically, this means that administering Tdap to a person who has not received a series of DTaP or DTP, or whose DTaP history is unknown, is an off-label use of the vaccine. You know that we strongly discourage off-label use of any vaccine unless that use is specifically endorsed by ACIP. Fortunately, ACIP has addressed this issue in their provisional recommendations. All adolescents should have documentation of having received an age-appropriate series of pediatric DTaP, DTP, or DT, or adult Td. Persons without documentation of this should receive a series of three vaccinations. The preferred schedule is a single dose of Tdap, followed by a dose of Td at least 4 weeks after the Tdap dose, and a second dose of Td at least 6 months after the Td dose. Although this is the preferred schedule, Tdap may be substituted for any one of the 3 Td doses in the series.

You will encounter adolescents who completed the recommended childhood vaccination series for tetanus and diphtheria toxoids with pediatric DT or adult Td vaccine rather than pediatric DTP or DTaP. That is, they received diphtheria and tetanus toxoids but no pertussis vaccine. ACIP recommends that these persons generally should receive Tdap according to the routine recommendations for adolescents.

The recommendation for vaccination of adolescents who have not received a complete series of pediatric pertussis vaccination is to administer ONE dose of Tdap. Do **not** administer two or three doses of Tdap vaccine. We must await more data and a change in the labeling of the vaccines to do this.

For the definitive clinical trials that led to licensure of both Boostrix and Adacel, the Tdap products were compared to standard adult Td for immunogenicity and safety of the Td component. They were compared to pediatric trials of DTaP for immunogenicity of the pertussis vaccine component. The safety profile of both vaccines was comparable to that of Td. As expected, the most common adverse reactions reported in both Tdap and Td recipients were local reactions, such as pain and redness at the site of injection. The proportion of recipients reporting these reactions was basically the same in both the Tdap and Td groups. No unusual or unexpected adverse reactions were identified for either vaccine.

The contraindications and precautions for Tdap are different than those for either pediatric DTaP or adult Td. As with **all** vaccines, a severe allergic reaction to a vaccine component or following a prior dose is a contraindication to subsequent doses. If this occurs an allergy workup should be considered to determine which component might be responsible. This is to avoid unnecessarily labeling the person as allergic to tetanus and diphtheria toxoids, booster doses of which will be needed for the rest of the person's life. The second contraindication is encephalopathy within 7 days of administration of a pertussis vaccine that is not attributable to another identifiable cause. This condition is a contraindication to pediatric DTaP but not to adult Td.

In addition to contraindications, there are several precautions for Tdap. I will remind you that if a precaution is present, the decision to vaccinate must be made based upon a case by case risk versus benefit consideration. The first precaution is a history of an Arthus-type reaction following a previous dose of tetanus or diphtheria toxoid containing vaccine. Persons who experienced an Arthus-type reaction following a prior dose of tetanus toxoid or Td usually have high serum tetanus or diphtheria antitoxin levels. These persons should **not** be given a dose of Td or Tdap more frequently than every 10 years, even if they have a tetanus-prone wound. A second precaution is a progressive neurological disorder, uncontrolled epilepsy, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized. If a decision is made to withhold pertussis vaccination, then Td may be used instead of Tdap. The third precaution is severe latex allergy. The tip and rubber plunger of the Boostrix prefilled syringe contain dry natural latex rubber. Boostrix in a prefilled syringes should not be administered to an adolescent with a history of a severe,

anaphylactic allergy to latex. A Boostrix prefilled syringe may be used for persons with less severe latex allergy, such as contact allergy to latex gloves. The Boostrix single dose vial and Adacel packaging do not contain latex. We believe that in the final document anaphylactic reaction to latex will be included as a contraindication, like it is for other severe allergic reactions to vaccine components. A history of Guillain Barré syndrome within 6 weeks after a previous dose of tetanus toxoid containing vaccine is a precaution to Tdap. This is also a precaution for other tetanus toxoid-containing vaccines. Finally, a moderate or severe acute illness with or without fever is a precaution, as it is with all other vaccines.

It is worth mentioning here that some conditions that are precautions to the use of pediatric DTaP are **not** precautions to the use of Tdap. ACIP believes that these conditions are unique to young children and are not expected to be an issue among adolescents. These conditions occasionally occurred following pediatric DTaP or DTP, but are **not** precautions for Tdap: temperature 105°F or higher, which is 40. 5°C, within 48 hours; collapse or shock-like state, also known as hypotonic hyporesponsive episode; persistent crying lasting 3 hours or longer; convulsions with or without fever, occurring within 3 days; and finally a history of an extensive limb swelling reaction. Other conditions that are **not** precautions to Tdap include a stable neurological disorder; pregnancy; breastfeeding; and immunosuppression, including persons with HIV infection. The immunogenicity of Tdap in persons with immunosuppression has not been studied and could be suboptimal. Finally, intercurrent minor illness and antibiotic use are not precautions to Tdap.

These provisional recommendations for the use of Tdap have been posted on the National Immunization Program website. The DTaP VFC resolution, which includes Tdap information, is posted on the ACIP website. We will have links to both pages on our broadcast resources and update web page.

The ACIP pertussis working group has begun work on recommendations for adults 19 years and older. We expect recommendations for adults in the next few months. In the mean time I will remind you that Adacel is approved by FDA for persons through age 64 years. You are certainly free to use Adacel for persons 19 through 64 years according to the approved uses listed in the package insert. I will remind you that both vaccines are approved for a **single** dose among persons who previously completed a series of pediatric DTP or DTaP.